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published in
Aging - Clinical and Experimental Research
2005

DOI (link to publisher)
10.1007/BF03324614

document version
Publisher's PDF, also known as Version of record

Change in serum albumin and subsequent decline in functional status in older persons

Bianca W.M. Schalk[1], Marjolein Visser[1], Brenda W.J.H. Penninx[1,2], Henk Baadenhuijsen[3], Lex M. Bouter[1], and Dorly J.H. Deeg[1]

[1]Institute for Research in Extramural Medicine (EMGO Institute), VU University Medical Center, Amsterdam, The Netherlands, [2]Sticht Center on Aging, Wake Forest University Health Sciences, Winston-Salem, USA, [3]Dutch Foundation for Quality Assessment in Clinical Laboratories (SKZL), University Medical Center Nijmegen, Nijmegen, The Netherlands

ABSTRACT. ***Background and aims:*** *This study examines whether a three-year change in serum albumin concentration is associated with subsequent decline in functional status in older persons.* ***Methods:*** *A total of 588 participants from the Longitudinal Aging Study Amsterdam aged 65-85 years were followed for six years. The three-year change in serum albumin was classified in four groups: chronic low (≤43 g/L at both time points), decrease (decrease of 2.4% or more) from normal to low, decrease but still normal, and stable normal albumin (reference group). During the subsequent three years, absolute change and a decline of one standard deviation or more (termed substantial decline) in functional status was assessed. Functional status was measured in two ways: using performance tests and self-reported functional ability.* ***Results:*** *Substantial decline in functional performance and functional ability was observed in 243 persons (41.3%) and 133 persons (22.6%), respectively. After adjustment for baseline functional status and potential confounders, chronic low albumin and a decrease from normal to low albumin were associated with a greater absolute decline in functional performance and in self-reported functional ability. Using the outcome substantial decline in functional status, only decrease to low serum albumin was associated with decline in functional ability [odds ratio (OR)=1.97; one-sided 95% Confidence Limit (CL)=1.09].* ***Conclusions:*** *This study indicates that chronic low serum albumin is a determinant of decline in functional status. However, a decrease in serum albumin from normal to low levels but within the normal range was a stronger determinant of future decline in functional status. Change in serum albumin level within the normal range measured between two points in time may be used as a general marker of future functional decline.*

(Aging Clin Exp Res 2005; 17: 297-305)

INTRODUCTION

Serum albumin level is commonly regarded as an indicator of nutrition (1, 2) and is known to predict morbidity and mortality in older persons (3, 4). Until now, few studies have investigated the association between serum albumin level and functional status. Two studies found a cross-sectional association between lower serum albumin concentration and limitations in activities of daily living (5, 6). Four longitudinal studies found that low serum albumin was associated with a higher incidence of disability (7, 8) and with decline in functional status (9). Although one study did find an association between low serum albumin (<38 g/L) and three-year functional decline, this association was not perceived with seven-year functional decline in high-functioning older persons (10). In a previous study based on the Longitudinal Aging Study Amsterdam (LASA), no association was found between low serum albumin (≤43 g/L) and three-year decline in functional performance (11).

To summarize, low serum albumin has been found to be associated with functional decline in some studies, but not in all. Most previous studies were based on a single measurement of serum albumin. It is hypothesized that albumin levels prior to the observed serum albumin level may explain the inconsistency in the literature. When two subsequent measurements of serum albumin are taken into account, two possibilities of having a low serum albumin can be distinguished: either the serum albumin level decreased, or it was already low and remained low.

Key words: Aging, albumin, functional status, prospective.

Correspondence: B.W.M. Schalk, MSc, EMGO Institute, VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands.
E-mail: DJH.Deeg@vumc.nl

Received February 23, 2004; accepted in revised form November 26, 2004.

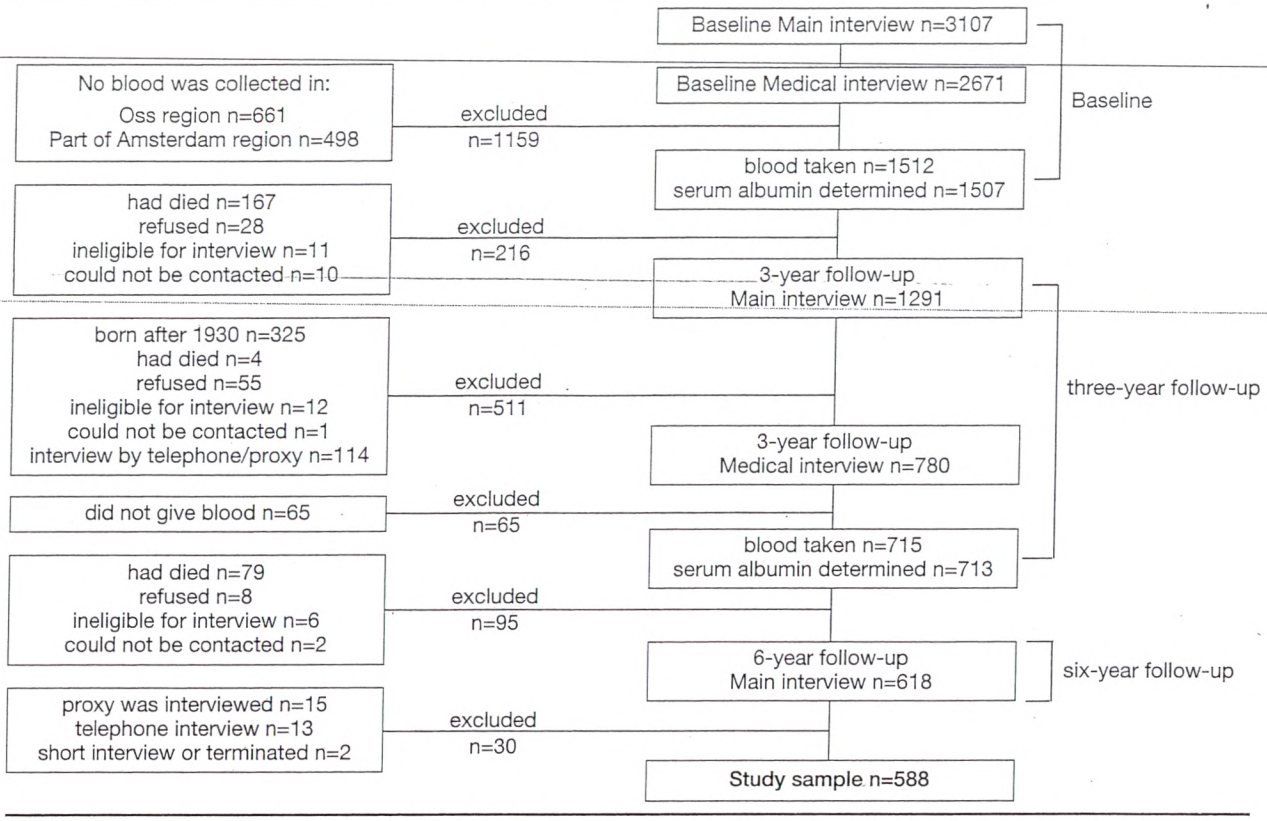

Fig. 1 - *Selection of study sample, Longitudinal Aging Study Amsterdam.*

We investigate here whether a decrease in serum albumin or a chronic low serum albumin level are responsible for the previously observed associations between low serum albumin and decline in functional status. To our knowledge, no previous studies have investigated whether a three-year change in serum albumin is related to subsequent change in functional status. Using this information, it would be possible to detect persons at risk for functional decline at an early stage, and prevent them from further decline. This is important, since functional decline may lead to deterioration in the quality of life, the institutionalization of older persons, and untimely death (12).

The majority of previous studies investigating the association between low serum albumin and functional status used self-reported measures of functional status rather than performance-based tests. Performance-based tests are objective measures, whereas self-reported measurements are to some extent influenced by mood or other personal factors (13). Since neither test measures the same construct, performance-based tests and self-reported measures may be considered as being complementary (14, 15), and both measures are used in the present study.

The present study examines whether a decrease in serum albumin concentration or chronic low serum albumin are associated with a change in functional status as assessed by functional performance tests and self-reported functional ability in an elderly community-dwelling population.

METHODS

Study sample

The LASA is an ongoing interdisciplinary longitudinal study that focuses on changes in physical, cognitive, emotional, and social functioning in the aging population in the Netherlands. Sampling and data collection have been described in detail elsewhere (16). Briefly, a sample of older men and women (aged 55-85 years), stratified by age, sex, urbanization, and expected five-year mortality, was drawn from the population registers of 11 municipalities in areas situated in the west (Amsterdam region), north-east (Zwolle region) and south (Oss region) of the Netherlands. At baseline (1992/93), and every three years thereafter, a new cycle of measurements was carried out. Each cycle consisted of a face-to-face main interview and a medical interview. Both interviews were carried out

at the subject's home by specially trained interviewers, during which the functional status of the interviewee was assessed. After the medical interview, a nurse interviewer collected blood samples. At the three-year follow-up, only respondents who participated in the main interview at follow-up and who were born before 1931 (aged 65 and older) were asked to participate in a second medical interview (17). Informed consent was obtained from all respondents. The study was approved by the Medical Ethics Committee of the VU University Medical Center in Amsterdam.

Figure 1 shows the selection of the sample relating to the present study.

Serum albumin

Non-fasting serum samples were obtained and analysed directly. In Zwolle, analyses were carried out in the laboratory of the ISALA Clinic (Location Weezelanden) at baseline and three years later, and in Amsterdam in the laboratory of the Valerius clinic at baseline and in the laboratory of the VU University Medical Center at three-year follow-up. To control for between-laboratory differences, we used information from the Dutch Foundation for Quality Assessment in Clinical Laboratories (SKZL). Every two months, eight serum samples were sent to the laboratories to be analyzed, and the serum albumin concentration was reported to the SKZL. Using linear regression, a regression line was fitted using the individual laboratory assessment of serum albumin for each sample and the overall national mean of the same sample. Separate lines were fitted for each laboratory, both at baseline and at three-year follow-up. Using regression equations, we adjusted serum albumin levels in LASA data.

Serum albumin concentrations (g/L) were determined using a bromcresol green (BCG) photometric assay in the laboratory in Zwolle, and at baseline in Amsterdam. At three-year follow-up, the laboratory of the VU University Medical Center used a bromcresol purple (BCP) method. To make serum albumin levels comparable, the levels determined with the BCP method were converted using a validated formula (18). The coefficient of variation of serum albumin was less than 2%.

Change in serum albumin was calculated as (T1-T0/T0)*100 (T0=serum albumin level at baseline 1992/93, and T1=serum albumin level at three-year follow-up 1995/96). The cut-off point for low serum albumin was based on 43 g/L, because no single person had a concentration of 38 g/L (19) at baseline or at three-year follow-up, and because the cut-off point of 43 g/L, which is within the normal range, had been used in previous studies (11, 20). The cut-off point of 2.4% for albumin change was based on the lowest quartile of change in serum albumin in the total study sample. Thus, change in serum albumin was classified into four categories: chronic low (albumin ≤43 g/L at T0 and T1), decrease from normal to low (2.4% decrease or more and albumin at T0>43 g/L and T1≤43 g/L), decrease but still normal (2.4% decrease or more and albumin at T0 and T1>43 g/L), and stable normal albumin (decrease less than 2.4% and albumin at T0 and T1>43 g/L=reference group).

Functional status

Functional status was measured at three- and six-year follow-ups by two different measures: functional performance and self-reported functional ability.

Functional performance. Functional performance was measured using three performance-based tests: walking, repeated chair stands, and putting on and taking off a cardigan (21). For the walking test, participants were asked to walk 3 meters, to turn around and to walk back 3 meters as quickly as possible. This test was timed and scored according to quartiles based on the entire LASA cohort at three-year follow-up (22): unable (score 0); ≥10 seconds (score 1); 8-9 seconds (score 2); 7 seconds (score 3); and ≤6 seconds (score 4). For repeated chair stands, participants were asked to fold their arms across their chest and to stand up five times from a kitchen chair. Time needed was categorized similarly: unable (score 0); ≥16 seconds (score 1); 13-15 seconds (score 2); 11-12 seconds (score 3); and ≤10 seconds (score 4). The time taken to put on and take off a cardigan was categorized as: unable (score 0); ≥16 seconds (score 1); 12-15 seconds (score 2); 10-11 seconds (score 3); and ≤9 seconds (score 4). Each performance test thus gave a score ranging from 0 to 4. The sum score provided the overall performance score and ranged from 0 to 12, with moderate reliability (Cronbach's alpha=0.63 at three-year follow-up and 0.74 at six-year follow-up). A lower score indicated poorer functional status. The sum score has been used before and predicts nursing home admission, mortality, hospitalization, and subsequent disability (14, 15, 22).

Functional ability. Functional ability was assessed with a six-item self-report questionnaire and was based on the ability to perform the following activities (23-25): walking up and down a staircase of 15 steps without stopping; dressing and undressing oneself; sitting down and rising from a chair; cutting one's own toenails; walking outside the house for 5 minutes; and use of own means of transport or public transport. Response categories ranged from 1 "not able to do the activity" to 5 "no difficulty". The sum score provides the overall functional ability score and ranged from 6 to 30, with good reliability (Cronbach's alpha=0.75 at three-year follow-up and 0.82 at six-year follow-up). A lower score indicates poorer functional status.

Covariates

Covariates were selected when referred to as potential confounders in the literature, and included age, sex, education (low, middle [reference] and high), smoking status

(never [reference], former, current), alcohol consumption (none [reference], 1-2 drinks daily, more than 2 drinks daily) and smoking (never [reference], former, current). Physical activity (minutes per week) in the previous two weeks was based on the following activities: walking outside, cycling, light and heavy household activities, and a maximum of two sports activities. Body mass index (BMI) was computed as weight in kilograms divided by height in meters squared. Self-reports of chronic diseases included diabetes mellitus, peripheral artery disease (PAD), cardiac disease, stroke, hypertension, pulmonary disease, arthritis, and cancer. Serum total cholesterol (mMol/L) was measured using the enzymatic colorimetry method with a Hitachi analyser, and serum creatinin (μmol/L) was measured using the Jaffé alkaline picrate reaction. For depressive symptoms, the Center for Epidemiologic Studies Depression (CES-D) scale was used (26) and a score of ≥16 was considered to indicate depression (27). Cognitive functioning was measured using the Mini-Mental State Examination (MMSE) and a score of ≤23 indicated cognitive impairment (28). All covariates were assessed at the three-year follow-up. Covariates were missing for some persons: alcohol consumption (n=1), physical activity (n=7), cognitive impairment (n=1), BMI (n=1) and total cholesterol (n=9).

Statistical analyses

All analyses were performed using SPSS 10.1. The outcome variable change in functional status was used as both a continuous and dichotomous variable. First, absolute

Table 1 - *General characteristics at three-year follow-up of 588 older persons according to subsequent three-year substantial decline in functional status.*

Characteristics	Functional performance			Functional ability		
	Substantial decline (n=243)	No decline (n=312)	*p*-value	Substantial decline (n=133)	No decline (n=437)	*p*-value
Sex, male, n (%)	117 (48.1)	151 (48.4)	0.95	56 (42.1)	221 (50.6)	0.09
Age (yr), mean (SD)	73.8 (6.0)	73.9 (6.1)	0.91	76.1 (6.1)	73.2 (5.9)	0.00
Education, n (%)			0.42			0.03
Low	136 (56.0)	190 (60.9)		91 (68.4)	243 (55.6)	
Middle	81 (33.3)	88 (28.2)		32 (24.1)	142 (32.5)	
High	26 (10.7)	34 (10.9)		10 (7.5)	52 (11.9)	
Smoking, n (%)			0.34			0.29
Never	85 (35.0)	116 (37.2)		56 (42.1)	152 (34.8)	
Former	109 (44.9)	148 (47.4)		55 (41.4)	209 (47.8)	
Current	49 (20.2)	48 (15.4)		22 (16.5)	76 (17.4)	
Alcohol consumption (drinks/d) n (%)			0.24			0.00
None	46 (19.0)	71 (22.8)		45 (34.1)	80 (18.3)	
<2 drinks	92 (38.0)	98 (31.4)		41 (31.1)	154 (35.2)	
≥2 drinks	104 (43.0)	143 (45.8)		46 (34.8)	203 (46.5)	
BMI (kg/m^2), mean (SD)	27.1 (4.3)	26.9 (3.9)	0.52	27.8 (4.4)	26.7 (4.0)	0.00
Physical activity (min/wk), mean (SD)	156.9 (109.6)	157.5 (96.7)	0.95	147.8 (92.4)	161.4 (104.7)	0.19
Prevalent diabetes, n (%)	20 (8.2)	14 (4.5)	0.07	18 (13.5)	18 (4.1)	0.00
Prevalent PAD, n (%)	17 (7.0)	28 (9.0)	0.40	14 (10.5)	33 (7.6)	0.28
Prevalent cardiac disease, n (%)	52 (21.4)	79 (25.3)	0.28	42 (31.6)	91 (20.8)	0.01
Prevalent stroke, n (%)	14 (5.8)	18 (5.8)	1.0	14 (10.5)	21 (4.8)	0.02
Prevalent hypertension, n (%)	48 (19.8)	68 (21.9)	0.54	33 (24.8)	86 (19.7)	0.21
Prevalent pulmonary disease, n (%)	29 (11.9)	41 (13.1)	0.67	23 (17.3)	52 (11.9)	0.11
Prevalent arthritis, n (%)	108 (44.4)	147 (47.1)	0.53	78 (58.6)	187 (42.8)	0.00
Prevalent cancer, n (%)	27 (11.1)	30 (9.6)	0.57	19 (14.3)	45 (10.3)	0.20
Cognitive impairment, n (%)	17 (7.0)	15 (4.8)	0.28	12 (9.1)	23 (5.3)	0.11
Depressive symptoms, n (%)	26 (10.7)	52 (16.7)	0.05	31 (23.7)	52 (12.0)	0.00
Creatinin (μmol/L), mean (SD)	89.7 (19.1)	91.5 (19.8)	0.31	92.7 (26.0)	90.3 (18.2)	0.23
Total cholesterol (mmol/L), mean (SD)	5.9 (1.2)	6.0 (1.1)	0.63	5.9 (1.0)	5.9 (1.1)	0.93
Functional performance, mean (SD)	8.7 (2.3)	7.1 (2.7)	0.00	6.5 (2.6)	8.1 (2.6)	0.00
Functional ability, mean (SD)	27.9 (3.2)	27.5 (4.2)	0.25	25.9 (4.5)	28.0 (3.6)	0.00

BMI: body mass index, PAD: peripheral artery disease. Substantial decline in functional status was defined as a decline of one standard deviation or more.

change in functional status score (functional performance and functional ability) was calculated as the functional status score at six-year follow-up minus the same score at three-year follow-up. Second, substantial decline in functional status was defined as a decline of one standard deviation or more. The standard deviation of change in the functional performance sum score was 2, and that in the functional ability sum score was 3 (22).

The association of substantial decline in functional status with the confounding variables at three-year follow-up was tested with a chi-square or *t*-test. Statistical significance was considered present at the two-sided *p*-value of 0.05.

When examining the association between change in serum albumin and functional status, one-sided statistical tests were performed at the *p*-value of 0.05. The reason for using the one-sided *p*-value was that we had a one-sided hypothesis on an unfavorable effect of chronic low serum albumin and a decrease in serum albumin, respectively. The differences across albumin categories of mean absolute change and substantial decline in functional status score were examined with the chi-square test and analyses of variance. Additionally, the difference in mean absolute change between the stable normal group and the other albumin categories was examined with the Bonferroni *post-hoc* test. The *p*-value of the two-sided statistical test in the output from the statistical package was divided by two to obtain a one-sided *p*-value.

Multivariate linear regression models were used to examine the relationship between change in serum albumin and absolute change in functional status score. Logistic regression models were used to examine the association between change in serum albumin and substantial functional decline. Results are presented as OR or regression coefficient with one-sided 95 percent confidence limits (95% CL). The presentation of confidence intervals is avoided because one-sided confidence intervals have either zero or infinity as the endpoint. The one-sided 95% CL was calculated by hand using a z-score of 1.65 instead of 1.96, which is used for two-sided tests. To take regression to the mean into account, all regression models were first adjusted for functional status at three-year follow-up. The second model also included covariates which at $p<0.20$ were associated with change in serum albumin and either substantial decline in functional performance or functional ability. Effect-modification was examined by testing the interaction between the potential covariates and change in serum albumin, explaining absolute change or substantial decline in functional status.

RESULTS

The respondents in the present study sample (n=588) had better cognitive status, lower level of education, higher BMI, higher overall performance score, higher overall functional ability score, and lower serum creatinin concentration, were younger, more were of the female gender, and they reported the presence of heart disease, pulmonary disease or PAD at three-year follow-up ($p<0.05$) less often than excluded persons (n=95 + 30=125, see Fig. 1). Of the excluded persons, 18.4% had chronic low serum albumin, 10.4% decreased to low serum albumin, 16.0% decreased but still had normal albumin levels, and 55.2% had stable normal albumin levels.

Of the 588 respondents, 106 persons (18.0%) had chronic low serum albumin, 54 (9.2%) decreased to low serum albumin, and 73 (12.4%) decreased but still had normal albumin levels. In total, 243 persons (41.3%) showed a substantial decline in functional performance, and 133 (22.6%) showed a substantial decline in functional ability. Of the 537 persons who had both measures of functional status, 61 persons (11.4%) showed a substantial decline in both measures.

Table 1 shows that persons who declined in functional performance had fewer depressive symptoms compared with the group with no decline. Substantial decline in functional ability was associated with lower alcohol consumption and higher BMI. Furthermore, per-

Table 2 - *Three-year change in serum albumin concentration in relation to subsequent three-year absolute change in functional status and substantial decline in functional status.*

	Functional performance (n=555)			Functional ability (n=570)		
Change in serum albumin*	**n**	**Mean change (SD)**	**Substantial decline % (n)**	**n**	**Mean change (SD)**	**Substantial decline % (n)**
Chronic low	101	-1.54 (2.62)	46.5 (47)	99	-1.70 (3.72)	27.3 (27)
Decrease to low	51	-1.90 (2.32)†	52.9 (27)	50	-2.12 (3.35)	38.0 (19)
Decrease but still normal	69	-1.13 (2.21)	42.0 (29)	72	-1.17 (2.86)	19.4 (14)
Stable normal	334	-0.94 (2.48)	41.9 (140)	349	-1.03 (2.97)	20.9 (73)
Overall p-value		0.01	0.23		0.03	0.02

Substantial decline in functional status was defined as a decline of one standard deviation or more. Change in functional status was defined as six-year follow-up score minus three-year follow-up score. *For definition of albumin categories, see Methods: Serum albumin. †$p<0.05$ *vs* stable normal group (Bonferroni *post-hoc* test).

Table 3 - *Three-year change in functional status according to previous change in serum albumin.*

Change in serum albumin*	Functional performance (n=555)		Functional ability (n=570)	
	β (95% CL)†	β (95% CL)‡	β (95% CL)†	β (95% CL)‡
Chronic low	**-0.80 (-0.37)**	**-0.65 (-0.22)**	**-0.64 (-0.05)**	**-0.63 (-0.04)**
Decrease to low	**-1.02 (-0.46)**	**-0.83 (-0.28)**	**-1.06 (-0.28)**	**-0.79 (-0.01)**
Decrease but still normal	-0.06 (0.44)	-0.25 (0.24)	-0.15 (0.52)	-0.36 (0.30)
Stable normal	reference	reference	reference	reference

Linear regression with independent variable albumin categories (*vs* stable normal albumin group) and with dependent variable: change in functional status; change in functional status was defined as six-year follow-up score minus three-year follow-up score. β: regression coefficient; 95% CL: one-sided 95% confidence limit. *For definition of albumin categories see Methods: Serum albumin. †Adjusted for functional status at three-year follow-up; ‡adjusted for functional status, age, sex, body mass index, physical activity, smoking, alcohol consumption, stroke, hypertension, diabetes mellitus and cognitive impairment at three-year follow-up.

sons who declined in functional ability were older, less educated, and reported stroke, diabetes, heart disease and arthritis more often, as well as having more depressive symptoms.

The mean change in functional performance and ability differed by serum albumin category (Table 2). Persons with a decrease to low albumin showed a significantly greater decline in functional performance compared with the stable normal albumin group ($p_{bonferroni\ test}=0.03$), and tended to show a greater decline in functional ability compared with the stable normal group ($p_{bonferroni\ test}=0.07$). No significant results were found ($p_{bonferroni\ test}>0.10$) for the other change in albumin categories. For substantial decline in functional performance, no significant differences across serum albumin categories were found, but the categories did differ in substantial decline in functional ability (Table 2).

Table 3 shows multiple linear regression models examining the relationship between change in serum albumin and absolute change in functional status. The chronic low group and the decrease to low serum albumin group had a significantly greater absolute decline in functional performance scores compared with the stable normal albumin group. Similar results were found for functional ability. No significant interactions between potential covariates and change in serum albumin were found.

Table 4 shows the multiple logistic regression models of change in serum albumin and substantial decline in functional status. Decrease to low albumin was associated with an increased risk of substantial decline in functional performance. This association was found to be no longer statistically significant after being additionally adjusted for potential confounders. When substantial decline in

Table 4 - *Three-year substantial decline in functional status according to previous change in serum albumin concentration.*

Change in serum albumin*	Functional performance (n=555)		Functional ability (n=570)	
	OR (95% CL)†	OR (95% CL)‡	OR (95% CL)†	OR (95% CL)‡
Chronic low	1.40 (0.94)	1.28 (0.83)	1.28 (0.82)	1.40 (0.88)
Decrease to low	**1.71 (1.01)**	1.42 (0.81)	**2.16 (1.25)**	**1.97 (1.09)**
Decrease but still normal	0.91 (1.45)	1.09 (0.66)	1.02 (0.59)	1.26 (0.71)
Stable normal	1.00	1.00	1.00	1.00

Logistic regression with dependent variable: substantial decline in functional status; substantial decline in functional status was defined as a decline of one standard deviation or more. OR: odds ratio; 95% CL: one-sided 95% confidence limit. *For definition of the albumin categories see Methods: Serum albumin. †Adjusted for functional status at three-year follow-up; ‡adjusted for functional status, age, sex, body mass index, physical activity, smoking, alcohol consumption, stroke, hypertension, diabetes mellitus and cognitive impairment at three-year follow-up.

functional ability was examined as outcome variable, persons with a decrease to low serum albumin showed an increased risk (OR 1.97; 95% CL 1.09) compared with the stable normal albumin group. No associations were found for chronic low serum albumin or for decrease but still normal albumin.

DISCUSSION

This community-based study shows that change in serum albumin levels within the normal range is associated with subsequent risk of functional decline. Persons with a decrease to low (≤43 g/L) albumin level especially seemed to have an increased risk.

Several studies, but not all, have found an association between low serum albumin and decline in functional status. We hypothesized that the albumin level preceding the low serum albumin level may explain the conflicting results. Our study showed that persons with a decrease to low serum albumin consistently showed an increased risk of decline in self-reported functional ability, while the association with chronic low albumin levels was less consistent. Thus, our hypothesis that the history of serum albumin may influence the association between low serum albumin and subsequent functional decline is confirmed.

Another explanation for the conflicting results of earlier studies may be the use of functional ability as outcome measure. Studies that did find an association used self-reported measures or evaluations by a geriatrician, whereas studies that did not find an association used substantial decline in functional performance or performance-test-related questions. In our study, both measures of functional status were used, since they complement each other (14, 15) and we found an association only for functional ability. An additional explanation for conflicting results in earlier studies may be the use of functional status in analyses: continuous or dichotomous. When we used a dichotomised outcome variable – as most other studies did – only persons with a decrease to low albumin levels showed an increased risk. When using absolute change in functional status score as the outcome, persons with chronic low serum albumin also experienced a greater decline in functional status score compared with the stable normal albumin group. This indicates that these persons may be at risk for some decline in functional status score, but do not satisfy the strict criteria of substantial decline in functional status. Thus, the method for assessing functional status, and how the functional status variable is used in analyses may also explain the inconsistency in the literature.

Low serum albumin concentration is commonly defined as levels of 38 g/L or below (19). Since not a single participant had an albumin concentration below 38 g/L at baseline or three years later, we used 43 g/L as the cut-off point for (chronic) low serum albumin concentration (20). In a population-based cohort study in a developed country such as The Netherlands (1, 2), serum albumin concentrations are likely to be higher compared with hospitalized patients or nursing-home residents. It is striking that, even at these higher albumin levels, which were within the normal range, clear associations between change in albumin and subsequent decline in functional status were observed. Furthermore, excluded persons (n=95+30=125, see Fig. 1) showed a greater decrease in serum albumin (2.4% or more) than the study sample. This may have produced underestimation in the results.

Several biological mechanisms for the observed associations may be hypothesized. One explanation might be the inflammation status of the body. Inflammation is accompanied by the release of pro-inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor α (29), which induce an acute-phase response, including a decrease in serum albumin (1, 29). Acute and chronic diseases are associated with inflammation (1). Furthermore, the presence of chronic diseases, such as stroke and coronary heart disease, has been observed to cause a decline in functional status (30). Thus, chronic diseases are associated with a decrease in serum albumin and functional status. Nevertheless, after adjustment for chronic disease and other health-related factors, we still observed a relationship between albumin and decline in functional status. Slightly more robust results were even found after adjustment for both baseline diseases and incident diseases between baseline and three-year follow-up (data not shown). However, we cannot exclude the possibility that a decrease in serum albumin represents sub-clinical disease, which would increase the risk of decline in functional status. Another potential explanation for the observed association may be that low serum albumin is an indicator of poor nutritional status (1, 2). Adjusting for BMI did not change our findings, nor did adjusting for body weight change parallel to albumin change (data not shown). However, other nutritional components may still affect functional decline. Another possible mechanism is sarcopenia. Low serum albumin is associated with lower muscle mass (31). Loss of muscle mass and strength is defined as sarcopenia, which is a determinant of poor physical function (32). It should be borne in mind that, rather than one single mechanism, an interrelation of several mechanisms together may explain the association between serum albumin and functional decline.

Variables such as BMI, physical activity, stroke, hypertension, diabetes mellitus, depression, and cognitive impairment were treated as potential confounders, but they may also mediate the relationship between albumin change and decline in functional status. For example, it may be hypothesized that poor nutritional status causes a reduction in physical activity, leading to

a decline in functional performance. Adjusting for these variables may have resulted in underestimation of the observed associations.

In our study, we used two albumin assessments separated by a period of three years. Future studies should examine whether albumin changes during a shorter time interval are also associated with future functional decline. For practical use, these studies should determine which absolute or relative threshold changes in serum albumin concentration are still, or no longer, markers of decline in functional status. Nutritional intervention or anti-inflammatory drugs may help to raise serum albumin levels above that threshold and prevent future functional decline. However, it is also important to consider other interventions, such as physical activity training (33), which are known to prevent or delay functional decline (34).

CONCLUSIONS

In this community-based study, we investigated whether a three-year change in serum albumin was associated with subsequent changes in functional performance and functional ability in older persons. Results confirm that chronic low serum albumin within the normal range is associated with a decline in functional status. However, only low serum albumin caused by a decrease in serum albumin was associated with substantial decline in functional status. These results suggest that a decrease in serum albumin, based on two measurements taken at different periods in time, may be used as an early marker of future functional decline.

ACKNOWLEDGEMENTS

The Longitudinal Aging Study Amsterdam (LASA) is funded by the Dutch Ministry of Health, Welfare and Sports, and the Vrije Universiteit in Amsterdam.

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